Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

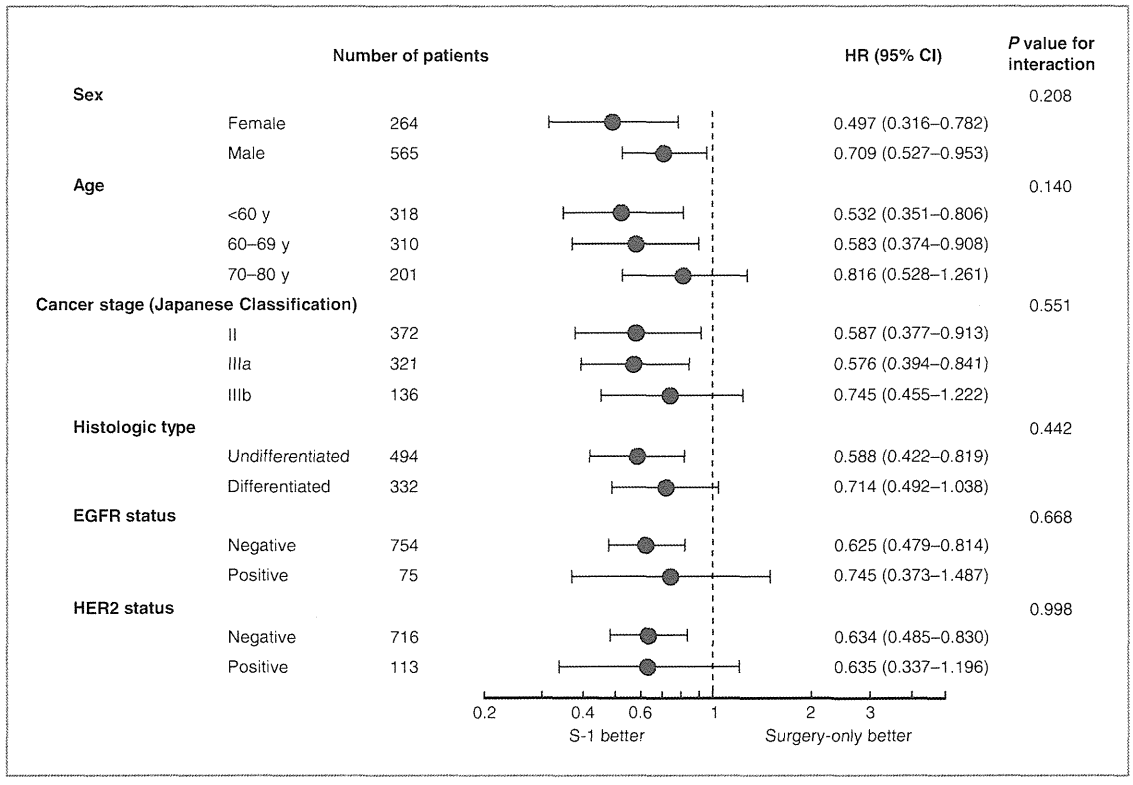

Figure 3. Subgroup analysis for OS. In the surgery-only group, cancers could not be classified as differentiated or undifferentiated in 3 patients.

that EGFR status should be evaluated in future clinical trials of EGFR-targeted agents. S-1 combined with EGFR/HER2-targeted agents merits further investigation in patients with gastric cancer.

Disclose of Potential Conflicts of Interest

A. Ochiai: commercial research grant, Taiho Pharmaceutical Co.; Ltd., other commercial research support, Chugai; and consultant/advisory board, Roche Diagnostic. W. Ichikawa: honoraria from speakers bureau, Taiho Pharmceutical Co., Ltd. H. Katai: commercial research grant and honoraria from speakers bureau, Taiho Pharmaceutical Co. Ltd. T. Sano: honoraria from speakers bureau, Taiho Pharmaceutical Co. Ltd. and Chugai Pharmaceutical. The funding source of this study had no role in the study design, data collection, data analysis, or interpretation.

Authors' Contributions

Conception and design: M. Terashima, K. Kitada, A. Ochiai, W. Ichikawa, M. Sasako
Development of methodology: A. Ochiai, M. Sasako
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Kitada, A. Ochiai, S. Sakuramoto, H. Katai, T. Sano, H. Imamura, M. Sasako
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Terashima, K. Kitada, A. Ochiai, W. Ichikawa, I. Kurahashi
Writing, review, and/or revision of the manuscript: M. Terashima, K. Kitada, W. Ichikawa, H. Katai, T. Sano, M. Sasako
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Kitada, H. Katai, T. Sano, M. Sasako
Study supervision: M. Terashima, A. Ochiai

Acknowledgments

The authors dedicate this article to the memory of Prof. Tetsuro Kubota, who contributed to the conception and design of the study. The authors thank the patients and their families, and the investigators from the 65 institutions for their cooperation. The authors also thank Prof. J. Patrick Barron, Chairman of the Department of International Medical Communications, Tokyo Medical University (Tokyo, Japan), a remunerated consultant of Taiho Pharmaceutical Co., Ltd., for his review of this report.

Grant Support

This study was funded by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan).
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 22, 2012; revised September 4, 2012; accepted September 4, 2012; published OnlineFirst September 12, 2012.

References

1. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin DM. Cancer incidence and mortality worldwide: IARC Cancer Base No. 10. GLOBOCAN. Lyon, France: International Agency for Research on Cancer; 2008. [cited 2012 Mar 20]. Available from: http://globocan.iarc.fr/factsheet.asp.

Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

2. Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 1996;7:548–57.
3. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810–20.
4. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011;29:4387–93.
5. Garcia I, Vizoso F, Martin A, Sanz L, Abdel-Lah O, Raigoso P, et al. Clinical significance of the epidermal growth factor receptor and HER2 receptor in resectable gastric cancer. Ann Surg Oncol 2003;10: 234–41.
6. Hayashi M, Inokuchi M, Takagi Y, Yamada H, Kojima K, Kumagai J, et al. High expression of HER3 is associated with a decreased survival in gastric cancer. Clin Cancer Res 2008;14:7843–9.
7. Kim MA, Lee HS, Lee HE, Jeon YK, Yang HK, Kim WH. EGFR in gastric carcinomas: prognostic significance of protein overexpression and high gene copy number. Histopathology 2008;52:738–46.
8. Begnami MD, Fukuda E, Fregnani JH, Nonogaki S, Montagnini AL, da Costa WL Jr, et al. Prognostic implications of altered human epidermal growth factor receptors (HERs) in gastric carcinomas: HER2 and HER3 are predictors of poor outcome. J Clin Oncol 2011;29: 3030–6.
9. Yasui W, Hata J, Yokozaki H, Nakatani H, Ochiai A, Ito H, et al. Interaction between epidermal growth factor and its receptor in progression of human gastric carcinoma. Int J Cancer 1988;41:211–7.
10. Okines A, Cunningham D, Chau I. Targeting the human EGFR family in esophagogastric cancer. Nat Rev Clin Oncol 2011;8:492–503.
11. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–97.
12. Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes-A systematic review. Int J Cancer 2012;130:2845–56.
13. Kim JS, Kim MA, Kim TM, Lee SH, Kim DW, Im SA, et al. Biomarker analysis in stage III-IV (M0) gastric cancer patients who received curative surgery followed by adjuvant 5-fluorouracil and cisplatin chemotherapy: epidermal growth factor receptor (EGFR) associated with favourable survival. Br J Cancer 2009;100:732–8.
14. Hofmann M, Stoss O, Shi D, Buttner R, Van de Vijver M, Kim W, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 2008;52:797–805.
15. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med 2007;131:18–43.
16. Ceppi P, Volante M, Novello S, Rapa I, Danenberg KD, Danenberg PV, et al. ERCC1 and RRM1 gene expressions but not EGFR are predictive of shorter survival in advanced non-small-cell lung cancer treated with cisplatin and gemcitabine. Ann Oncol 2006;17:1818–25.
17. Matsubara J, Yamada Y, Nakajima TE, Kato K, Hamaguchi T, Shirao K, et al. Clinical significance of insulin-like growth factor type 1 receptor and epidermal growth factor receptor in patients with advanced gastric cancer. Oncology 2008;74:76–83.
18. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—2nd English edition. Gastric Cancer 1998;1: 10–24.
19. Luber B, Deplazes J, Keller G, Walch A, Rauser S, Eichmann M, et al. Biomarker analysis of cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric and oesophago-gastric junction cancer: results from a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO). BMC Cancer 2011;11:509.
20. Lordick F, Luber B, Lorenzen S, Hegewisch-Becker S, Folprecht G, Wöll E, et al. Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Br J Cancer 2010;102: 500–5.
21. Sartore-Bianchi A, Moroni M, Veronese S, Carnaghi C, Bajetta E, Luppi G, et al. Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with panitumumab. J Clin Oncol 2007;25:3238–45.
22. Di Fiore F, Sesboue R, Michel P, Sabourin JC, Frebourg T. Molecular determinants of anti-EGFR sensitivity and resistance in metastatic colorectal cancer. Br J Cancer 2010;103:1765–72.
23. Chung KY, Shia J, Kemeny NE, Shah M, Schwartz GK, Tse A, et al. Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. J Clin Oncol 2005;23:1803–10.
24. Park SR, Kook MC, Choi IJ, Kim CG, Lee JY, Cho SJ, et al. Predictive factors for the efficacy of cetuximab plus chemotherapy as salvage therapy in metastatic gastric cancer patients. Cancer Chemother Pharmacol 2010;65:579–87.
25. Kimura M, Tsuda H, Morita D, Ichikura T, Ogata S, Aida S, et al. A proposal for diagnostically meaningful criteria to classify increased epidermal growth factor receptor and c-erbB-2 gene copy numbers in gastric carcinoma, based on correlation of fluorescence *in situ* hybridization and immunohistochemical measurements. Virchows Arch 2004;445:255–62.
26. Janjigian YY, Werner D, Pauligk C, Steinmetz K, Kelsen DP, Jäger E, et al. Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. Ann Oncol. Epub 2012 Jun 11.
27. Tanizaki J, Okamoto I, Takezawa K, Tsukioka S, Uchida J, Kiniwa M, et al. Synergistic antitumor effect of S-1 and HER2-targeting agents in gastric cancer with HER2 amplification. Mol Cancer Ther 2010;9: 1198–207.
28. Kobunai T, Watanabe T, Fukusato T. Antitumour activity of S-1 in combination with cetuximab on human gastric cancer cell lines *in vivo*. Anticancer Res 2011;31:3691–6.

World J Surg (2012) 36:2637–2643
DOI 10.1007/s00268-012-1721-y

World Journal of Surgery

Survival Benefit of Palliative Gastrectomy in Gastric Cancer Patients with Peritoneal Metastasis

Masanori Tokunaga · Masanori Terashima · Yutaka Tanizawa · Etsuro Bando · Taiichi Kawamura · Hirofumi Yasui · Narikazu Boku

Published online: 21 July 2012

Abstract
Background The survival benefit of palliative gastrectomy in patients with peritoneal metastasis as a single incurable factor remains unclear.
Methods A total of 148 gastric cancer patients with peritoneal metastasis underwent gastrectomy or chemotherapy at the Shizuoka Cancer Center between September 2002 and December 2008 and were included in this study. The effects of gastrectomy and chemotherapy on their long-term outcome were investigated. Multivariate analysis was also performed to identify independent prognostic factors.
Results Gastrectomy was performed in 82 patients and subsequent chemotherapy was administered to 55. Chemotherapy was selected as an initial treatment for 66 patients. Median survival time (MST) was identical between patients with and without gastrectomy (13.1 vs. 12.0 months; $P = 0.410$). Conversely, MST was significantly longer in patients who received chemotherapy (13.7 months) than those who did not (7.1 months; $P = 0.048$). According to the results of multivariate analysis, chemotherapy (hazards ratio [HR] = 0.476; 95 % CI = 0.288–0.787) was selected as an independent prognostic factor, while gastrectomy was not.
Conclusions The results of the present study did not show a survival benefit of palliative gastrectomy in selected patients with peritoneal metastasis. Instead, chemotherapy has to be considered as an initial treatment for these patients.

M. Tokunaga (✉) · M. Terashima · Y. Tanizawa · E. Bando · T. Kawamura
Division of Gastric Surgery, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: m.tokunaga@scchr.jp

H. Yasui · N. Boku
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

Introduction

Gastric cancer is diagnosed frequently and is the second leading cause of cancer-related deaths in Japan [1]. Although the long-term outcome of early gastric cancer is good, that of advanced gastric cancer is dismal, particularly when combined with other incurable factors [2–4]. Recent advances in chemotherapy have improved the survival rate of gastric cancer patients with incurable factors. However, survival rates remain limited and there is still room for improvement in the survival rate [5, 6].

The incurable factors observed frequently in patients with advanced gastric cancer are peritoneal, liver, and distant lymph node metastases [7, 8]. Better survival rates were reported in Japan following gastrectomy plus metastasectomy if the incurable factors were liver or para-aortic lymph node metastases and if the surgery was curative [9–12]. In contrast, curative resections are difficult in patients with widespread peritoneal metastasis, which is the most frequently observed incurable factor [13–16]. Although a few surgeons have reported the efficacy of performing a peritonectomy, this concept has not been accepted widely, even in Japan [17].

Previously, a number of authors investigated the feasibility of palliative gastrectomy in patients with incurable factors [14, 18–24]. However, each study included patients with a range of incurable factors; therefore, the effect of gastrectomy in selected patients with peritoneal metastasis remains unclear. The aim of the present study was to clarify the effects of gastrectomy on gastric cancer patients

with peritoneal metastasis. The appropriate treatment strategy in patients with localized peritoneal metastasis was also investigated.

Materials and methods

Patients

Between September 2002 and December 2008, 279 gastric cancer patients with peritoneal metastasis underwent gastrectomy or chemotherapy at the Shizuoka Cancer Center, Japan. Of these, 131 patients had incurable factors other than peritoneal metastasis so the remaining 148 patients with no other obvious incurable factors were included in this study. Pathological examination of biopsy specimens from the stomach revealed adenocarcinoma in all patients. Patients who had received any previous treatment for gastric cancer were not included in the present study. Peritoneal metastasis was diagnosed histopathologically in patients who underwent laparotomy (106 patients) or was diagnosed clinically using computed tomography in patients who did not undergo laparotomy (42 patients).

The patients' characteristics and surgical and pathological findings were collected retrospectively from our prospectively recorded database and individual patient records. The patients' clinicopathological characteristics were analyzed, and survival curves were compared according to the treatment modalities administered (gastrectomy and chemotherapy). Multivariate analysis was also conducted to identify independent prognostic factors.

This study followed ethical guidelines for human subjects and was approved by the institutional review board of the Shizuoka Cancer Center.

Pretreatment examinations

Computed tomography (CT) with contrast medium was performed as a routine pretreatment examination in all patients except those with poor renal function or with an allergy to the contrast medium. Patients were regarded as having clinically evident peritoneal metastasis (cP+) if the CT findings showed obvious peritoneal metastasis which included massive ascites, cirrhosal implants of the intra-abdominal area or on the small or large bowel, remarkably increased visceral fat density, and omental metastasis. If CT did not show any obvious peritoneal metastasis, patients were regarded as not having clinically evident peritoneal metastasis (cP−).

Macroscopic type was classified according to the Japanese Gastric Cancer Association (JGCA) classification system [25]. Histological type was also classified according to the JGCA classification system, in which tubular and papillary adenocarcinoma are defined as differentiated adenocarcinoma, while poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma are defined as undifferentiated adenocarcinoma.

The degree of peritoneal metastasis was classified in patients who underwent laparotomy as follows: P0, no implants to the peritoneum; P1, cancerous implants to the region directly adjacent to the stomach peritoneum (above the transverse colon), including the greater omentum; P2, several scattered metastases to the distant peritoneum and ovarian metastasis alone; and P3, numerous metastases to the distant peritoneum [26].

Indications for gastrectomy

In patients with P1, gastrectomy was performed if macroscopic curative resection was expected. Gastrectomy was also selected as an initial treatment in patients with tumor-associated symptoms such as bleeding or gastric outlet obstruction even if curative resection could not be expected. If patients had P2 or P3 peritoneal metastasis and they did not have tumor-associated symptoms, gastrectomy would not be performed in principle.

Statistics

All continuous data are presented as the median (range). Survival rates were calculated using the Kaplan–Meier method, and the log-rank test was used to compare the groups. In this study, overall survival time was defined as time from initial treatment (surgery or chemotherapy) to any death, including noncancer-related death.

Independent prognostic factors were identified using the Cox proportional hazards model. In the analysis, each patient's age (<60 or ≥ 60 years old), sex, clinically evident peritoneal metastasis (cP− or cP+), gastrectomy (performed or not performed), chemotherapy (received or not received), Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 or 2, 3), macroscopic type (type 4 or other), and histology (differentiated or undifferentiated) were included as covariates. The Bonferroni test was used during multiple comparisons. A P value <0.05 was considered significant. All statistical analyses were conducted using R version 2.13.1.

Results

The patient characteristics are indicated in Table 1. Macroscopic type 3 tumors were observed in 43 % of the patients and type 4 tumors were observed in 39 %. Tumors were undifferentiated in three-fourths of the patients. The pretreatment ECOG performance status was generally good

(≤1) and was 2 or higher in 10 % of patients. Gastrectomy was performed in 82 patients and subsequent chemotherapy was administered to 55 of these patients. Chemotherapy was selected as an initial treatment in 66 patients. We also compared the background data between patients according to the treatment provided. There were no differences between any two groups with respect to sex, ECOG performance status, histology, and macroscopic type. The median age was significantly different between the groups, with patients who received gastrectomy only the oldest followed by patients who received both gastrectomy and chemotherapy. The incidence of clinically evident peritoneal metastasis was significantly higher in patients who underwent chemotherapy only than in those who underwent gastrectomy only or both gastrectomy and chemotherapy.

Table 2 lists the treatments provided. Of the 82 patients who underwent gastrectomy, total gastrectomy was performed more frequently (67 %) than distal gastrectomy (33 %). S1-based chemotherapy was the most frequently selected treatment regimen in this study. Of 121 patients who received chemotherapy, second-line chemotherapy was given in 64 % of patients and third-line chemotherapy was administered in 35 % of patients.

Figure 1 shows the overall survival curve of all patients. Of the 148 patients, 137 were followed until their death. Median follow-up period of survivors was 29.7 months. One-year and three-year overall survival rates were 53.9 and 18.1 %, respectively. Figure 2a shows the overall survival curves of patients with and without gastrectomy. The median survival time (MST) of patients with gastrectomy was 13.1 months ($n = 82$) and that without gastrectomy was 12.0 months ($n = 66$; $P = 0.410$). Overall survival curves of patients who did or did not receive chemotherapy are shown in Fig. 2b. MST was significantly longer in patients who received chemotherapy (13.7 months; $n = 121$) than in those who did not (7.1 months; $n = 27$; $P = 0.048$).

Table 3 shows the results of the Cox proportional hazards model. Chemotherapy [hazards ratio (HR) = 0.476; 95 % CI = 0.288–0.787], ECOG performance status 0 or 1(HR = 0.278; 95 % CI = 0.156–0.495), and macroscopic tumor types other than type 4 (HR = 0.566; 95 % CI = 0.377–0.848) were selected as independent prognostic factors, while gastrectomy was not selected.

Table 1 Patient characteristics

		Gastrectomy	Chemotherapy	Gastrectomy + chemotherapy
Number (*n*)	148	27	66	55
Age (years)[a]	65 (20–85)	77 (53–85)	60 (20–77)	67 (34–76)
Sex (*n*)				
Male	90	18	36	36
Female	58	9	30	19
Performance status (*n*)				
0 or 1	133	23	58	52
2 or 3	15	4	8	3
Histology (*n*)				
Differentiated	36	7	20	9
Undifferentiated	112	20	46	46
Macroscopic type (*n*)				
≠type 4	90	19	35	36
type 4	58	8	31	19
Clinically evident peritoneal metastasis[b]				
Yes (cP+)	62	2	51	9
No (cP)	86	25	15	46
Gastrectomy (*n*)				
Yes	82	27	0	55
No	66	0	66	0
Chemotherapy (*n*)				
Yes	121	0	66	55
No	27	27	0	0

[a] The differences between each group are statistically significant ($P < 0.0167$ between any two groups)

[b] The difference is statistically significant between patients who underwent chemotherapy and those who underwent gastrectomy. It is also statistically significant between patients who underwent chemotherapy and those who underwent gastrectomy + chemotherapy

Table 2 Treatments provided

Gastrectomy	82
Total gastrectomy	55
Distal gastrectomy	27
Chemotherapy	121
5-FU	8
S1	43
S1/CDDP	27
MTX/5-FU	28
CPT11/CDDP	5
Others	10
Number of regimens administered	
1st line	44
2nd line	35
3rd line	24
4th line	16
5th line	1
6th line	1

FU fluorouracil, *CDDP* cisplatin, *MTX* methotrexate, CPT11 irinotecan

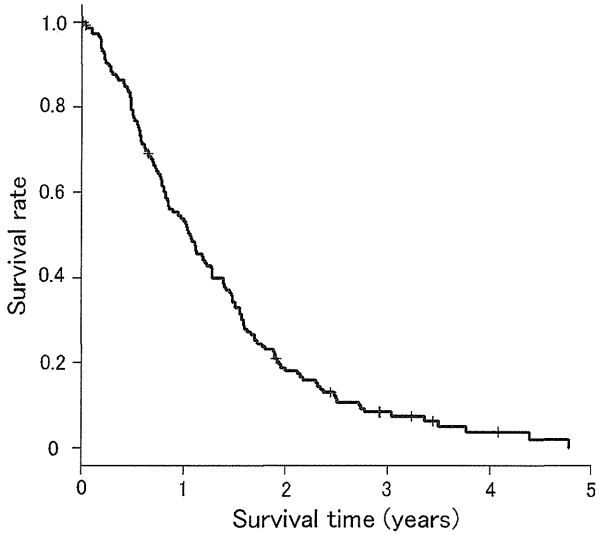

Fig. 1 Survival curves of patients included in this study. MST is 390 days. One- and three-year survival rates are 53.9 and 18.1 %, respectively

Investigation of 40 patients with localized peritoneal metastasis (P1)

The degree of peritoneal metastasis was confirmed by laparotomy in 106 of the 148 patients: it was P1 in 40 patients, P2 in 12 patients, and P3 in 54 patients. Survival analysis was conducted in 40 patients with P1 peritoneal metastasis. R0 resection according to 6th edition of the TNM classification was performed in 18 patients and the MST for these patients (26.4 months) was longer than that of the 16 patients who underwent R1 or R2 gastrectomy (Fig. 3, 12.3 months; $P < 0.001$) [27].

Discussion

Recent advances in chemotherapy regimens have improved the survival rates of gastric cancer patients with incurable factors. Koizumi et al. [5] reported an MST of 13 months in patients with advanced gastric cancer who were treated with S1 and cisplatin, and Bang et al. [6] reported a 13.8 month median overall survival time in patients with HER2-positive advanced gastric cancer who were treated with trastuzumab plus chemotherapy. However, to date, the effects of chemotherapy are limited and the 5 year survival rate of patients with unresectable gastric cancer remains grim [5, 6].

The feasibility of palliative gastrectomy in patients with unresectable gastric cancer is under debate [14, 18–24]. Many studies have examined a variety of patients with gastric cancer; however, the type and the number of incurable factors differed among patients. To the best of our knowledge, the present study is the first report that investigates a similar group of patients who all had peritoneal metastasis but did not have other obvious incurable factors. Therefore, we were able to identify the appropriate treatment strategy for patients with peritoneal metastasis with less bias than the previous studies.

The present study showed that there was no survival benefit associated with palliative gastrectomy. Instead, we recommend chemotherapy, as long as patients do not have tumor-associated symptoms. Sarela et al. [13, 14], and Kahlke et al. [20] also did not recommend palliative gastrectomy if patients did not have tumor-associated symptoms because it did not affect the patient's survival time. In contrast, Kim et al. [19] and Li et al. [23] recommended palliative gastrectomy, and Lin et al. [28] recommended palliative gastrectomy with subsequent chemotherapy to improve the survival rate of patients.

Multivariate analysis identified pretreatment ECOG performance status, macroscopic tumor type, and chemotherapy as independent prognostic factors. Macroscopic tumor type 4 is a widely accepted prognostic factor, and the incidence of peritoneal metastasis associated with type 4 tumors is higher than with other macroscopic tumor types [3, 4, 22]. Poor ECOG performance status is also a well-known independent prognostic factor in advanced malignancies [13, 16, 20]. Sarela et al. [13] reported that poor ECOG performance status is an independent prognostic factor in patients with peritoneal metastasis, as found in our study.

We also investigated the efficacy of R0 surgery in patients with localized peritoneal metastasis and found that

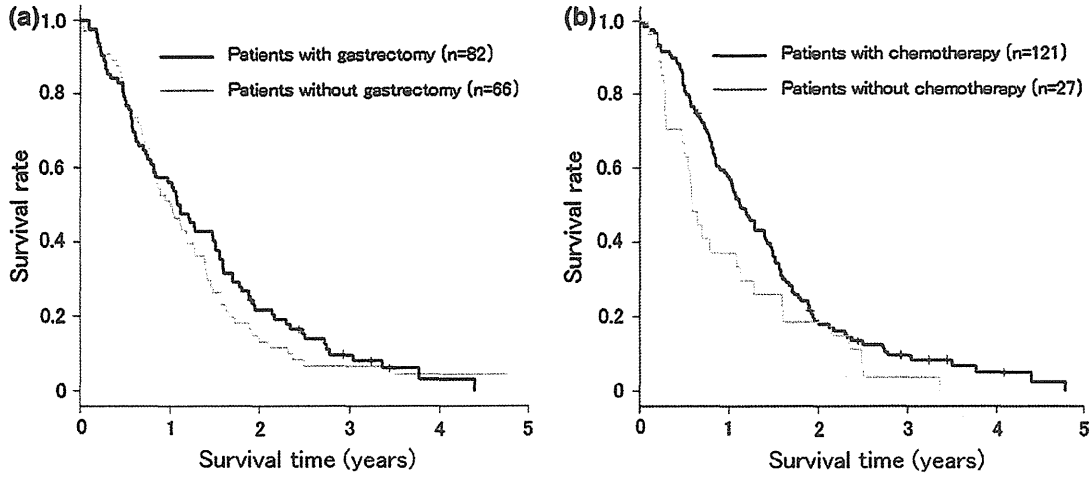

Fig. 2 **a** Survival curves of patients with or without gastrectomy. There is no difference in MST between patients with gastrectomy (13.1 months; $n = 82$) and those without gastrectomy (12.0 months; $n = 66$; $P = 0.410$). **b** Survival curves of patients who received or did not receive chemotherapy. MST was significantly longer for patients who received chemotherapy (13.7 months; $n = 121$) than for those who did not (7.1 months; $n = 27$; $P = 0.048$)

Table 3 Results of multivariate analysis

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (<60 years vs. ≥60 years)	0.830	1.045	0.700–1.559
Sex (male vs. female)	0.516	0.879	0.596–1.297
cP (cP− vs. cP+)	0.122	0.681	0.419–1.108
Gastrectomy (yes vs. no)	0.897	1.031	0.646–1.647
Chemotherapy (yes vs. no)	0.004	0.476	0.288–0.787
ECOG performance status (0,1 vs. 2,3)	<0.001	0.278	0.156–0.495
Macroscopic type (≠type 4 vs. type 4)	0.006	0.566	0.377–0.848
Histology (differentiated vs. undifferentiated)	0.290	0.466	0.454–1.256

ECOG Eastern Cooperative Oncology Group

the survival rate was better in patients who were able to undergo curative resection than those who were not. Ouchi et al. [18] segregated patients according to the degree of peritoneal metastasis (P1 vs. P2 or P3) because they believed that the tumor load must also be taken into account. Moreover, Hioki et al. [29] reported a better outcome in patients with localized peritoneal metastasis following gastrectomy than in those with widespread peritoneal metastasis, and emphasized that patients with a good performance status and localized peritoneal metastasis should be considered appropriate surgical candidates. Based on the results from these reports it may be plausible to distinguish whether patients have localized or widespread peritoneal metastases in order to establish the appropriate treatment strategy for these patients.

However, it has been reported that the accuracy of computed tomography for diagnosing peritoneal metastasis is limited, and the degree of peritoneal metastasis would not be diagnosed without laparotomy [30]. Recently, the feasibility of diagnostic laparoscopy, which is less invasive than laparotomy and more sensitive for finding peritoneal metastasis than computed tomography, was reported [31, 32]. In our institute, we also perform this procedure in patients in whom a high incidence of peritoneal metastasis was estimated. However, we began diagnostic laparoscopy in the middle of 2008 so most of the patients in the present series did not receive diagnostic laparoscopy before treatment.

There are limitations associated with this retrospective study. These include a possible bias in the selection of treatment strategies, including chemotherapeutic regimens and indication for gastrectomy, and the possibility that patient backgrounds differ between groups. In fact, patient age and the incidence of clinically evident peritoneal metastasis were different between groups. Therefore, we conducted multivariate analysis including these factors as covariates. To overcome these problems and to obtain conclusive results, a well-designed prospective trial is necessary. Groups in Japan and Korea are currently collaborating on an international randomized controlled trial

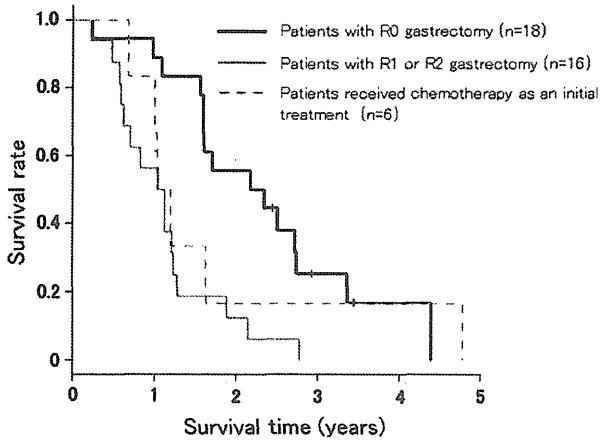

Fig. 3 Survival curves of 40 patients with localized peritoneal metastasis confirmed by laparotomy. MST was significantly longer in 18 patients who underwent R0 gastrectomy (26.4 months) than in 16 patients who underwent R1 or R2 gastrectomy (12.3 months; $P < 0.001$). MST for 18 patients with R0 gastrectomy was also longer than that for six patients who received chemotherapy as an initial treatment (12.5 months), although this was not statistically significant ($P = 0.414$)

investigating the efficacy of gastrectomy in gastric cancer patients with a single incurable factor. Therefore, we must await the results of this study, although the patients being investigated in the prospective study are not identical to those included in the present study [33].

In the present study, we used overall survival to evaluate the efficacy of each treatment. We could not evaluate patient quality of life after treatment, the burden of care, and cost because it was difficult to collect these data retrospectively. However, these factors should also be taken into account, particularly in patients with incurable disease [34]. If poor quality of life and increased burden of care were observed in patients who had undergone gastrectomy, they would further reinforce the arguments against gastrectomy in patients having peritoneal metastasis.

In conclusion, the results of the present study did not show a survival benefit with palliative gastrectomy in patients with peritoneal metastasis. Instead, chemotherapy has to be considered an initial treatment for these patients. We still have to await the result of randomized controlled trial being performed in the East to address this specific issue.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55(2):74–108
2. Kakeji Y, Maehara Y, Tomoda M et al (1998) Long-term survival of patients with stage IV gastric carcinoma. Cancer 82(12): 2307–2311
3. Isobe Y, Nashimoto A, Akazawa K et al (2011) Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. Gastric Cancer 14(4):301–316
4. Maruyama K, Kaminishi M, Hayashi K et al (2006) Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric Cancer 9(2):51–66
5. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9(3): 215–221
6. Bang YJ, Van Cutsem E, Feyereislova A et al (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376(9742):687–697
7. Maehara Y, Hasuda S, Koga T et al (2000) Postoperative outcome and sites of recurrence in patients following curative resection of gastric cancer. Br J Surg 87(3):353–357
8. Sakuramoto S, Sasako M, Yamaguchi T et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357(18):1810–1820
9. Koga R, Yamamoto J, Ohyama S et al (2007) Liver resection for metastatic gastric cancer: experience with 42 patients including eight long-term survivors. Jpn J Clin Oncol 37(11):836–842
10. Sakamoto Y, Ohyama S, Yamamoto J et al (2003) Surgical resection of liver metastases of gastric cancer: an analysis of a 17-year experience with 22 patients. Surgery 133(5):507–511
11. Shirabe K, Wakiyama S, Gion T et al (2006) Hepatic resection for the treatment of liver metastases in gastric carcinoma: review of the literature. HPB (Oxford) 8(2):89–92
12. Tokunaga M, Ohyama S, Hiki N et al (2010) Can super extended lymph node dissection be justified for gastric cancer with pathologically positive para-aortic lymph nodes? Ann Surg Oncol 17(8):2031–2036
13. Sarela AI, Miner TJ, Karpeh MS et al (2006) Clinical outcomes with laparoscopic stage M1, unresected gastric adenocarcinoma. Ann Surg 243(2):189–195
14. Sarela AI, Yelluri S (2007) Gastric adenocarcinoma with distant metastasis: is gastrectomy necessary? Arch Surg 142(2):143–149 discussion 149
15. Hartgrink HH, Putter H, Klein Kranenbarg E et al (2002) Value of palliative resection in gastric cancer. Br J Surg 89(11): 1438–1443
16. Kim KH, Lee KW, Baek SK et al (2011) Survival benefit of gastrectomy +/− metastasectomy in patients with metastatic gastric cancer receiving chemotherapy. Gastric Cancer 14(2):130–138
17. Yonemura Y, Kawamura T, Bandou E et al (2005) Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Br J Surg 92(3):370–375
18. Ouchi K, Sugawara T, Ono H et al (1998) Therapeutic significance of palliative operations for gastric cancer for survival and quality of life. J Surg Oncol 69(1):41–44
19. Kim DY, JooJK Park YK et al (2008) Is palliative resection necessary for gastric carcinoma patients? Langenbecks Arch Surg 393(1):31–35
20. Kahlke V, Bestmann B, Schmid A et al (2004) Palliation of metastatic gastric cancer: impact of preoperative symptoms and the type of operation on survival and quality of life. World J Surg 28(4):369–375. doi:10.1007/s00268-003-7119-0
21. Doglietto GB, Pacelli F, Caprino P et al (2000) Surgery: independent prognostic factor in curable and far advanced gastric cancer. World J Surg 24(4):459–463. doi:10.1007/s002689910073 discussion 464
22. Yook JH, Oh ST, Kim BS (2005) Clinicopathological analysis of Borrmann type IV gastric cancer. Cancer Res Treat 37(2):87–91

23. Li C, Yan M, Chen J et al (2010) Survival benefit of non-curative gastrectomy for gastric cancer patients with synchronous distant metastasis. J Gastrointest Surg 14(2):282–288
24. Chang YR, Han DS, Kong SH et al (2012) The value of palliative gastrectomy in gastric cancer with distant metastasis. Ann Surg Oncol 19(4):1231–1239
25. Japanese Gastric Cancer Association (1998) Japanese Classification of Gastric Carcinoma—2nd English Edition. Gastric Cancer 1(1):10–24
26. Japanese Research Society for Gastric Cancer (1995) Japanese classification of gastric carcinoma, 1st English edn. Kanehara & Co, Tokyo
27. Sobin L, Wittekind D (eds) (2002) TNM classification of malignant tumors, vol 6. Wiley, New York
28. Lin SZ, Tong HF, You T et al (2008) Palliative gastrectomy and chemotherapy for stage IV gastric cancer. J Cancer Res Clin Oncol 134(2):187–192
29. Hioki M, Gotohda N, Konishi M et al (2010) Predictive factors improving survival after gastrectomy in gastric cancer patients with peritoneal carcinomatosis. World J Surg 34(3):555–562. doi: 10.1007/s00268-010-0396-5
30. Kim SJ, Kim HH, Kim YH et al (2009) Peritoneal metastasis: detection with 16- or 64-detector row CT in patients undergoing surgery for gastric cancer. Radiology 253:407–415
31. Shim JH, Yoo HM, Lee HH et al (2011) Use of laparoscopy as an alternative to computed tomography (CT) and positron emission tomography (PET) scans for the detection of recurrence in patients with gastric cancer: a pilot study. Surg Endosc 25: 3338–3344
32. Tsuchida K, Yoshikawa T, Tsuburaya A et al (2011) Indications for staging laparoscopy in clinical T4M0 gastric cancer. World J Surg 35:2703–2709. doi:10.1007/s00268-011-1290-5
33. Fujitani K, Yang HK, Kurokawa Y et al (2008) Randomized controlled trial comparing gastrectomy plus chemotherapy with chemotherapy alone in advanced gastric cancer with a single non-curable factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01. Jpn J Clin Oncol 38(7):504–506
34. Russell RC, Treasure T (2012) Counting the cost of cancer surgery for advanced and metastatic disease. Br J Surg 99:449–450

J Gastrointest Surg (2012) 16:1854–1859
DOI 10.1007/s11605-012-1981-8

ORIGINAL ARTICLE

Postoperative Intra-abdominal Complications Assessed by the Clavien–Dindo Classification Following Open and Laparoscopy-Assisted Distal Gastrectomy for Early Gastric Cancer

Masanori Tokunaga · Junya Kondo · Yutaka Tanizawa · Etsuro Bando · Taiichi Kawamura · Masanori Terashima

Received: 12 June 2012 / Accepted: 19 July 2012 / Published online: 31 July 2012

Abstract
Background Laparoscopy-assisted gastrectomy (LAG) has been increasingly used for the treatment of early gastric cancer, and many advantages over open gastrectomy (OG) have been reported. However, only a few reports have assessed postoperative complications following LAG using the Clavien–Dindo classification.
Methods A total of 265 patients who underwent distal gastrectomy or pylorus-preserving gastrectomy with D1+ lymph node dissection for clinical stage IA early gastric cancer at the Shizuoka Cancer Center between June 2009 and December 2011 were included in this study. Clinicopathological characteristics and early surgical outcomes were compared between patients who underwent LAG (LAG group, $n=129$) and those who underwent OG (OG group, $n=136$). The severity of postoperative morbidities was assessed according to the Clavien–Dindo classification.
Results There were no differences in sex or age between the two groups. Body mass index (21.97 vs 23.19, $P<0.001$) was lower in the LAG group than the OG group. The duration of the postoperative hospital stay was similar between the two groups (9 days each, $P=0.511$). There was no difference in the overall morbidity rate (grade II or higher) between the two groups (LAG group, 7.0 %; OG group, 8.1 %; $P=0.818$). The incidence of grade IIIa or more severe morbidities was also not significantly different between the LAG group (4.7 %) and OG group (2.9 %, $P=0.532$).
Conclusions There was no significant difference in postoperative complication rates between the LAG and the OG groups. The more severe Clavien–Dindo grade III complications, which required surgical interventions, were observed at similar rates between the two groups. Laparoscopic gastrectomy for early gastric cancer is therefore feasible in terms of the incidence and severity of intra-abdominal complications.

Keywords Clavien–Dindo · Morbidity · LAG · Gastric cancer

Introduction

Laparoscopy-assisted gastrectomy (LAG) has been performed increasingly, particularly in Japan and Korea, where the incidence of early gastric cancer is higher than in Western countries. Several advantages of LAG compared to open gastrectomy (OG) have been reported, including less intraoperative bleeding, preserved postoperative respiratory function, early recovery of bowel movements, and better cosmetic results.[1–5]

However, several disadvantages are also associated with LAG, and these include prolonged operation times, technical difficulties, and high costs.[1,2,4] In addition, the safety of LAG is a contentious issue due to the absence of solid evidence from randomized controlled trials. To date, a number of retrospective studies and a few prospective studies have investigated and compared the incidence of postoperative complications following LAG

M. Tokunaga (✉) · J. Kondo · Y. Tanizawa · E. Bando · T. Kawamura · M. Terashima
Division of Gastric Surgery, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: m.tokunaga@scchr.jp

with those following OG.[6–11] However, most of these studies adopted their own subjective criteria to assess the postoperative complications, making it difficult to compare the complication rates between the studies.[6,7] The Clavien–Dindo classification uses objective criteria to assess the severity and incidence of postoperative complications. This classification system was first reported in 2004 and validated thereafter.[12,13]

The aim of the present study was to clarify the incidence and the severity of postoperative intra-abdominal complications following LAG using the Clavien–Dindo classification and to compare these with postoperative complications following OG.

Materials and Methods

A total of 287 patients underwent distal gastrectomy or pylorus-preserving gastrectomy with D1+ lymph node dissection for clinical stage IA early gastric cancer at the Shizuoka Cancer Center between June 2009 and December 2011. Fifteen of these patients underwent simultaneous surgery for other malignant diseases and were therefore excluded. Seven patients whose preoperative body mass index (BMI) were 30 or higher were also excluded. The remaining 265 patients were included in the present study.

The patients' characteristics, pathological findings, and surgical findings were collected from our database records and individual patient electronic medical records. The postoperative clinical course of each patient, including the incidence and severity of intra-abdominal infection complications, was collected from individual electronic medical records. Data collection and analysis were approved by the institutional review board of the Shizuoka Cancer Center.

Pathological tumor depth, nodal status, and curability of surgery were assessed according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours, seventh edition.[14]

Japanese gastric cancer treatment guidelines 2010 was used to designate the degree of lymph node dissection.[15,16]

Indications for LAG and OG

A distal or pylorus-preserving gastrectomy with D1+ lymph node dissection was performed if patients had clinical stage IA early gastric cancer located lower two-thirds of the stomach, which did not fulfill the criteria for endoscopic submucosal dissection.[15,16] LAG was not indicated for patients with a BMI over 30.0 throughout the study period; thus, all patients with a BMI over 30.0 underwent OG irrespective of their preferred approach.

Surgical Approaches for Patients with Early Gastric Cancer

Between June 2009 and March 2010, the surgical approach (open or laparoscopy) used to treat early gastric cancer was determined by the patient's preference. After preoperative examinations, surgeons explained the advantages and disadvantages of both LAG and OG, leaving the patients to decide on the surgical approach. During this period, 88 patients underwent distal or pylorus-preserving gastrectomy for early gastric cancer. A total of 41 patients chose open surgery and 47 patients chose laparoscopic surgery.

After April 2010, a randomized controlled trial comparing LAG and OG was undertaken in Japan (JCOG 0912 trial); thus, patients who fulfilled the inclusion criteria and agreed to participate in the study were randomly assigned to undergo LAG or OG (62 patients). Otherwise, patients chose the surgical approach they preferred (115 patients). During this period, 95 patients underwent open surgery and 82 patients underwent laparoscopic surgery.

All open surgeries were performed or supervised by one of five experienced surgeons in our institute, each of whom had performed more than 200 cases of open gastrectomy before the study period. Of these five surgeons, two also had much experience of laparoscopic surgery (more than 100 cases of LAG before the study) and had board certification by Japanese Society of Endoscopic Surgery. In this study, all laparoscopic surgeries were performed or supervised by one of these two board-certified surgeons.

Definition of Postoperative Intra-abdominal Complications

The postoperative intra-abdominal complications assessed in this study included pancreas-related infections, postoperative bleeding, anastomotic leakage, anastomotic stenosis, bowel obstruction, and wound infections observed within 30 days after the surgery.

The Clavien–Dindo classification was adopted to grade the severity of the postoperative intra-abdominal complication for each patient. According to the Clavien–Dindo classification, patients were classified as having grade II complications if medical treatment, such as antibiotic administration, was used. Patients were classified as grade IIIa if surgical intervention without general anesthesia was indicated, and classified as grade IIIb if surgical intervention under general anesthesia was indicated. If patients required admission to the intensive care unit, they were regarded as having grade IVa (with single organ dysfunction) or IVb (with multiorgan dysfunction) complications. Postoperative mortality was defined as a grade V complication.

In this study, patients with intra-abdominal complications classified as Clavien–Dindo grade II or higher were regarded as having complications. The incidence and

grade of each complication was recorded prospectively in medical records.

Comparison of Short-Term Outcomes Between LAG and OG

Of the 265 patients included in the present study, early surgical outcomes were compared between patients who underwent LAG (LAG group, $n=129$) and those who underwent OG (OG group, $n=136$).

Statistics

All continuous variables are presented as the median (range). Statistical analyses were performed using Fisher's exact test, the Student's t test, and the Mann–Whitney test. A P value less than 0.05 was considered significant. All statistical analyses were conducted using R Statistics version 2.13.1.

Results

Patient characteristics are shown in Table 1. There were no differences in sex or age between the two groups. The BMI was higher in the OG group than in the LAG group. All patients included in this study had preoperative clinical stage IA early gastric cancer. Surgical findings are indicated in Table 2. Pylorus-preserving gastrectomy was frequently performed in the LAG group although the difference was not statistically significant. Operation times were longer, and there was less intraoperative bleeding in the LAG group compared to the OG group. One patient in the both groups each required perioperative transfusions. The patient in the LAG group required a transfusion for intra-abdominal bleeding, and a re-operation was also required (grade IIIb). The reason for the transfusion in the OG group was intra-abdominal bleeding. The patients recovered well without additional treatment (grade II).

Pathological findings are shown in Table 3 and were not different between the two groups. All surgeries were designated as R0 resections according to the seventh edition of the UICC TNM Classification of Malignant Tumours.

Patient postoperative outcomes are described in Table 4. There was no difference in the duration of the postoperative hospital stay between the two groups. Overall morbidity rates (grade II or higher) were not different between the two groups (LAG group, 7.0 %; OG group, 8.1 %; $P=0.818$). The incidence of grade IIIa or more severe morbidities was also not significantly different between the LAG group (4.7 %) and OG group (2.9 %, $P=0.532$).

Table 1 Patient characteristics

	LAG group	OG group	*P* value
Number of patients	129	136	
Sex (*n*)			
Male	85	91	0.897
Female	44	45	
Age (years)			
Median	64	66	0.692
Range	19-88	33-84	
Body mass index (kg/m^2)			
Median	21.97	23.19	<0.001
Range	6.94–29.81	15.35–29.74	
Preoperative morbidities (*n*)			
Yes	50	62	0.266
No	79	74	
Previous laparotomy (*n*)			
Yes	43	48	0.796
No	86	88	

Discussion

The present study revealed no difference in the postoperative intra-abdominal complication rates between the LAG group and the OG group. In addition, there was no difference in the severity of complications as assessed by the Clavien–Dindo classification between the two groups.

The incidence of postoperative morbidity following laparoscopic gastrectomy has been reported as 4.7–25.3 %.[7,11,17–22] The heterogeneity between studies may be attributed to the differences in patient backgrounds, degree of lymph node

Table 2 Surgical findings of patients

	LAG group	OG group	*P* value
Operative procedure (*n*)			
DG	57	73	0.141
PPG	72	63	
Operation time (min)			
Median	225	202	<0.001
Range	146–400	102–318	
Bleeding (ml)			
Median	30.5	208	<0.001
Range	0–372	16–1,695	
Number of retrieved lymph nodes			
Median	42	45	0.257
Range	26–94	19–108	
Transfusion (*n*)	1	1	0.948

DG distal gastrectomy, *PPG* pylurus-preserving gastrectomy, *TG* total gastrectomy

Table 3 Pathological results of patients

	LAG group	OG group	*P* value
Tumor depth (*n*)			
T1 (m/sm)	118	129	0.470
T2 (mp)	8	4	
T3 (ss)	3	3	
T4 (se/si)	0	0	
Nodal status (*n*)			
N0	114	120	0.472
N1	10	14	
N2	4	1	
N3a	1	1	
N3b	0	0	
Pathological stage (*n*)			
Ia	107	119	0.063
Ib	13	11	
IIa	8	2	
IIb	0	3	
IIIa	0	1	
IIIb	1	0	
IIIc	0	0	
IV	0	0	

dissection, and criteria used to assess the severity of the complications.[7,11,17–22] The same heterogeneity is also observed following open gastrectomy, presumably due to the absence of widely accepted specific criteria to assess postoperative complications.

Table 4 Postoperative clinical course of patients

	LAG group	OG group	*P* value
Postoperative intra-abdominal complications (*n* (%))			
Pancreas-related infection	2 (1.6)	3 (2.2)	1.000
Bleeding	1 (0.8)	1 (0.7)	1.000
Intra-abdominal abscess	3 (2.3)	1 (0.7)	0.359
Anastomotic leakage	2 (1.6)	1 (0.7)	0.614
Anastomotic stenosis	2 (1.6)	1 (0.7)	0.614
Bowel obstruction	1 (0.8)	1 (0.7)	1.000
Wound infection	0 (0)	3 (2.2)	0.248
Severity of complications (*n*)			
Grade II	3 (2.3)	7 (5.1)	–
Grade IIIa	3 (2.3)	3 (2.2)	–
Grade IIIb	1 (0.8)	0 (0)	–
Grade IVa	2 (1.6)	1 (0.7)	–
Grade IVb	0 (0)	0 (0)	–
Grade V	0 (0)	0 (0)	–
Grade II or more severe (*n* (%))	9 (7.0)	11 (8.1)	0.818
Grade IIIa or more severe (*n* (%))	6 (4.7)	4 (2.9)	0.532
Postoperative hospital stay (days)			
Median	9	9	0.511
Range	6–71	6–49	

The Clavien–Dindo classification of surgical complications was first reported in 2004, and its utility has been validated by many reports.[12,13] Recently, the incidence of postoperative complications assessed by the Clavien–Dindo classification following LAG was reported.[20,21,23,24] Jiang et al. reported a 13.3 % overall incidence rate of Clavien–Dindo grade II or higher postoperative complications following LAG. However, the complication rate following OG was unclear in their series.[23] Lee et al. reported no difference in the incidence of postoperative complications assessed by the Clavien–Dindo classification following LAG compared to those following OG. In their series, 72.8 % of patients who underwent LAG had stage IA early gastric cancer and underwent a limited lymphadenectomy, while most patients who underwent OG had advanced disease and received D2 lymphadenectomy.[20] It is possible that the differences in tumor stages and degree of lymph node dissection affected the results. In the present study, therefore, we included patients who underwent distal or pylorus-preserving gastrectomy with D1+ lymph node dissection.

Most studies comparing early surgical outcomes between LAG and OG reported longer operation times and less intraoperative blood loss in the LAG group than in the OG group, and the same results were obtained in the present study.[1,2,4] The quality of lymph node dissection was assessed by comparing the number of harvested lymph nodes, and it is under debate whether the quality of lymph node dissection is identical between both approaches.[1,2,4] In this study, the number of harvested lymph nodes was not different between the groups; thus, we consider laparoscopic approach as feasible in terms of quality of D1+ lymph node dissection.

A surgeon's experience has been reported as being associated with postoperative morbidity and mortality following LAG. Surgeons require 30 to 50 cases to complete their learning curve.[17,25–27] In this study, all laparoscopic surgeries were performed or supervised by board-certified, experienced surgeons; thus, we consider that the surgeons' skill did not affect the results.

Currently, there are two ongoing multicenter randomized trials comparing LAG and OG in Japan and Korea. In the KLASS trial conducted in Korea, no difference in early surgical outcomes including morbidity rate has been reported, although the final results are not yet available.[7] In the KLASS trial, the definition and grade of each complication was not mentioned. A phase II trial in Japan, JCOG 0703, revealed the safety of LAG, and a subsequent randomized controlled trial, JCOG 0912, has already started.[6] In the JCOG 0912 trial, the Clavien–Dindo classification system is being used to assess each complication. The final results of these randomized trials are required to

conclude which procedure is best for patients with early gastric cancer in terms of postoperative complications.

The present retrospective study has some limitations. Firstly, patient characteristics were different between the groups, such as BMI. In our institute, laparoscopic surgery had not been indicated in patients with high BMI (>30), and all patients with high BMI (>30) were treated with open gastrectomy; thus, we excluded these patients to minimize the heterogeneity between the groups. However, the median BMI was still higher in the OG group than in the LAG group. It is unclear whether difference in BMI really affected the incidence of intra-abdominal complications.[28–30] Recently, Hiki et al. reported that a high BMI was not necessarily associated with a higher incidence of postoperative complications following LAG.[31] However, possible biases must be taken into account when interpreting the results of the present study. When the final results of the randomized controlled trials become available, the clinical relevance of LAG in the treatment of gastric cancer will become more apparent.

In conclusion, the present retrospective study revealed no significant difference in the postoperative complication rates between the LAG and the OG groups. The more severe Clavien–Dindo grade III complications, which required surgical interventions, were observed at a similar rate between the two groups. Therefore, the use of laparoscopic gastrectomy for the treatment of early gastric cancer is feasible from the viewpoint of the incidence and severity of intra-abdominal complications.

Disclosures We have no conflict of interest to be declared.

References

1. Kodera Y, Fujiwara M, Ohashi N, et al. Laparoscopic surgery for gastric cancer: a collective review with meta-analysis of randomized trials. J Am Coll Surg 2010; 211(5):677-86.
2. Memon MA, Khan S, Yunus RM, et al. Meta-analysis of laparoscopic and open distal gastrectomy for gastric carcinoma. Surg Endosc 2008; 22(8):1781-9.
3. Kawamura H, Yokota R, Homma S, Kondo Y. Comparison of respiratory function recovery in the early phase after laparoscopy-assisted gastrectomy and open gastrectomy. Surg Endosc 2010; 24 (11):2739-42.
4. Ohtani H, Tamamori Y, Noguchi K, et al. A meta-analysis of randomized controlled trials that compared laparoscopy-assisted and open distal gastrectomy for early gastric cancer. J Gastrointest Surg 2010; 14(6):958-64.
5. Kim YW, Baik YH, Yun YH, et al. Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. Ann Surg 2008; 248(5):721-7.
6. Katai H, Sasako M, Fukuda H, et al. Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703). Gastric Cancer 2010; 13(4):238-44.
7. Kim HH, Hyung WJ, Cho GS, et al. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report–a phase III multicenter, prospective, randomized Trial (KLASS Trial). Ann Surg 2010; 251(3):417-20.
8. Han JH, Lee HJ, Suh YS, et al. Laparoscopy-assisted distal gastrectomy compared to open distal gastrectomy in early gastric cancer. Dig Surg 2011; 28(4):245-51.
9. Zhao Y, Yu P, Hao Y, et al. Comparison of outcomes for laparoscopically assisted and open radical distal gastrectomy with lymphadenectomy for advanced gastric cancer. Surg Endosc 2011; 25 (9):2960-6.
10. Hwang SI, Kim HO, Yoo CH, et al. Laparoscopic-assisted distal gastrectomy versus open distal gastrectomy for advanced gastric cancer. Surg Endosc 2009; 23(6):1252-8.
11. Lee SI, Choi YS, Park DJ, et al. Comparative study of laparoscopy-assisted distal gastrectomy and open distal gastrectomy. J Am Coll Surg 2006; 202(6):874-80.
12. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250(2):187-96.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240 (2):205-13.
14. Sobin L, Gospodarowicz M, Wittekind C. TNM Classification of Malignant Tumors. 7th ed. . New York: Wiley-Blackwell 2009.
15. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011; 14: 113-123.
16. Sano T, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. Gastric Cancer 2011; 14: 97-100.
17. Kitano S, Shiraishi N, Uyama I, et al. A multicenter study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan. Ann Surg 2007; 245(1):68-72.
18. Obama K, Okabe H, Hosogi H, et al. Feasibility of laparoscopic gastrectomy with radical lymph node dissection for gastric cancer: From a viewpoint of pancreas-related complications. Surgery 2011 (149):15-21.
19. Kim MC, Kim W, Kim HH, et al. Risk factors associated with complication following laparoscopy-assisted gastrectomy for gastric cancer: a large-scale korean multicenter study. Ann Surg Oncol 2008; 15(10):2692-700.
20. Lee JH, Park DJ, Kim HH, et al. Comparison of complications after laparoscopy-assisted distal gastrectomy and open distal gastrectomy for gastric cancer using the Clavien–Dindo classification. Surg Endosc; in press.
21. Hwang SH, Park do J, Jee YS, et al. Risk factors for operative complications in elderly patients during laparoscopy-assisted gastrectomy. J Am Coll Surg 2009; 208(2):186-92.
22. Lee JH, Yom CK, Han HS. Comparison of long-term outcomes of laparoscopy-assisted and open distal gastrectomy for early gastric cancer. Surg Endosc 2009; 23(8):1759-63.
23. Jiang X, Hiki N, Nunobe S, et al. Postoperative outcomes and complications after laparoscopy-assisted pylorus-preserving gastrectomy for early gastric cancer. Ann Surg 2011; 253(5):928-33.
24. Jiang X, Hiki N, Nunobe S, et al. Postoperative pancreatic fistula and the risk factors of laparoscopy-assisted distal gastrectomy for early gastric cancer. Ann Surg Oncol 2012; 19(1):115-21.
25. Ryu KW, Kim YW, Lee JH, et al. Surgical complications and the risk factors of laparoscopy-assisted distal gastrectomy in early gastric cancer. Ann Surg Oncol 2008; 15(6):1625-31.
26. Kunisaki C, Makino H, Takagawa R, et al. Predictive factors for surgical complications of laparoscopy-assisted distal gastrectomy for gastric cancer. Surg Endosc 2009; 23(9):2085-93.

27. Kim W, Song KY, Lee HJ, et al. The impact of comorbidity on surgical outcomes in laparoscopy-assisted distal gastrectomy: a retrospective analysis of multicenter results. Ann Surg 2008; 248 (5):793-9.
28. Noshiro H, Shimizu S, Nagai E, et al. Laparoscopy-assisted distal gastrectomy for early gastric cancer: is it beneficial for patients of heavier weight? Ann Surg 2003; 238(5):680-5.
29. Yamada H, Kojima K, Inokuchi M, et al. Effect of obesity on technical feasibility and postoperative outcomes of laparoscopy-assisted distal gastrectomy–comparison with open distal gastrectomy. J Gastrointest Surg 2008; 12(6):997-1004.
30. Makino H, Kunisaki C, Izumisawa Y, et al. Effect of obesity on laparoscopy-assisted distal gastrectomy compared with open distal gastrectomy for gastric cancer. J Surg Oncol 2010; 102(2):141-7.
31. Hiki N, Fukunaga T, Yamaguchi T, et al. Increased fat content and body shape have little effect on the accuracy of lymph node retrieval and blood loss in laparoscopic distal gastrectomy for gastric cancer. J Gastrointest Surg 2009; 13(4):626-33.

JJCO Japanese Journal of Clinical Oncology

Clinical Trial Note

Jpn J Clin Oncol 2012;42(6)556–559
doi:10.1093/jjco/hys054
Advance Access Publication 23 April 2012

A Phase II Study of Systemic Chemotherapy with Docetaxel, Cisplatin, and S-1 (DCS) Followed by Surgery in Gastric Cancer Patients with Extensive Lymph Node Metastasis: Japan Clinical Oncology Group Study JCOG1002

Hiroshi Katayama[1], Seiji Ito[2,*], Takeshi Sano[3], Daisuke Takahari[4], Junki Mizusawa[1], Narikazu Boku[5], Akira Tsuburaya[6], Masanori Terashima[7], Mitsuru Sasako[8] and Stomach Cancer Study Group of the Japan Clinical Oncology Group

[1]Japan Clinical Oncology Group Data Center/Operations Office, Multi-institutional Clinical Trial Support Center, National Cancer Center, Tokyo, [2]Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, [3]GI Surgery Division, Cancer Institute Hospital, Tokyo, [4]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, [5]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, [6]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, [7]Division of Gastric Surgery, Shizuoka Cancer Center, Mishima and [8]Department of Surgery, Hyogo College of Medicine, Nishinomiya

*For reprints and all correspondence: Seiji Ito, Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. E-mail: seito@aichi-cc.jp

Received December 27, 2011; accepted March 16, 2012

A Phase II trial was initiated in Japan to evaluate the efficacy and safety of preoperative chemotherapy with docetaxel, cisplatin and S-1 for gastric cancer with extensive lymph node metastasis. Patients are eligible to participate in the study if they have para-aortic lymph node metastases (stations no. 16a2/16b1) and/or a bulky lymph node ($\geq$3 cm $\times$ 1 or $\geq$1.5 cm $\times$ 2) along the celiac, splenic, common or proper hepatic arteries or the superior mesenteric vein, while patients with other distant metastases are ineligible. A total of 50 patients will be enrolled over 2.5 years. The primary endpoint is the response rate of the preoperative chemotherapy, which will be assessed based on the Response Evaluation Criteria in Solid Tumors ver. 1.0. The secondary endpoints are %3-year survival, %5-year survival, proportion of patients with R0 resection, proportion of patients who complete the preoperative chemotherapy and surgery, proportion of patients who complete the protocol treatment, pathological response rate and adverse events. This trial was registered at the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/) as UMIN000006069.

Key words: gastric cancer – extensive lymph node metastasis – preoperative chemotherapy – Phase II

INTRODUCTION

Gastric cancer with extensive lymph node metastasis (ELM) is often unresectable. Furthermore, patients with gastric cancer and ELM often have a poor prognosis, even after an R0 resection. The Stomach Cancer Study Group of the Japan Clinical Oncology Group (SCSG/JCOG) has addressed this problem.

Since 2000, we have performed two Phase II trials (JCOG0001 and JCOG0405) to evaluate the preoperative chemotherapy followed by gastrectomy with D2 plus para-aortic lymph node dissection (PAND) for gastric cancer with ELM. In JCOG0001, the patients received two or three courses of irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1), and then underwent surgery.

This study showed a good %3-year survival of 27.0%, but was terminated because of three treatment-related deaths (TRDs) among 55 enrolled patients (1). To develop a safer and more effective treatment, we conducted JCOG0405, in which patients received two or three courses of cisplatin (60 mg/m^2 on day 8) and S-1 (80 mg/m^2 from days 1–21) (CS) as preoperative chemotherapy and then underwent surgery. This study also showed an excellent %3-year survival of 58.8% with no TRD and low toxicity (2). Preoperative chemotherapy with CS is highly promising and is considered the current standard treatment for gastric cancer patients with ELM in SCSG/JCOG.

JCOG9501 demonstrated that prophylactic PAND did not improve survival (3). However, an integrated analysis of JCOG0001 and JCOG0405 showed a greater therapeutic index (multiplication of frequency of lymph nodes metastasis by a 3-year survival rate) (4) of para-aortic lymph node than JCOG9501 even in patients with bulky lymph node without para-aortic lymph node preoperatively (JCOG0001: 4.3, JCOG0405: 12, JCOG9501: 2.7). Therefore, we adopted the same surgical procedure as in previous studies, D2 plus PAND, for all this population.

Recently, the addition of docetaxel to cisplatin and 5-FU was shown to improve the outcome of unresectable or recurrent gastric cancer patients in the USA and Europe (5). In Japan, several Phase I and Phase II trials have been conducted to evaluate a combination of docetaxel, cisplatin and S-1 (DCS) in patients with unresectable or recurrent gastric cancer (6–9). Although neutropenia and febrile neutropenia frequently occurred, the response rate was extremely high in each trial. Among several DCS regimens, we adopted the one used in the Phase II trial at Kitasato University (the Kitasato regimen) because this regimen was shown to have less toxicity and a higher response rate than other regimens. Here, we are conducting a multi-institutional Phase II trial (JCOG1002) to evaluate the efficacy and safety of DCS (the Kitasato regimen) as a preoperative chemotherapy for gastric cancer with ELM. If the efficacy and safety prove to be sufficient, we will conduct a Phase III trial to compare preoperative DCS with the current standard CS.

The JCOG Protocol Review Committee approved this study protocol in June 2011, and this study was activated in July 2011. This trial was registered at the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/) as UMIN000006069.

PROTOCOL DIGEST OF THE JCOG1002

Purpose

The aim of this study is to evaluate the efficacy and safety of DCS as a preoperative chemotherapy for gastric cancer with ELM.

Study Setting

A multi-institutional (50 specialized centers), single-arm Phase II trial.

Endpoints

The primary endpoint is the response rate to preoperative chemotherapy as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0. RECIST ver. 1.0 is used instead of ver. 1.1 because we will compare the results with previous studies using the same criteria. The secondary endpoints are %3-year survival, %5-year survival, proportion of patients with R0 resection, proportion of patients who complete the preoperative chemotherapy and surgery, proportion of patients who complete the protocol treatment, pathological response rate and adverse events.

Inclusion Criteria

(i) Histologically proven primary gastric adenocarcinoma
(ii) Contrast-enhanced abdominal computed tomography (CT; 10 mm or less of slice thickness) revealed one or both of the following:
  (a) Para-aortic lymph node metastasis $\geq$1.0 cm between the upper margin of the celiac artery and the upper border of the inferior mesenteric artery (stations no. 16a2/16b1)
  (b) Bulky lymph nodes ($\geq$3 cm × 1 or $\geq$1.5 cm × 2) along the celiac, splenic, common or proper hepatic arteries, or the superior mesenteric vein
(iii) Contrast-enhanced thoracic/abdominal/pelvic CT revealed none of the following:
  (a) Mediastinal lymph node metastasis
  (b) Lung metastasis
  (c) Peritoneal metastasis
  (d) Liver metastasis
  (e) Pleural effusion, ascites
  (f) Para-aortic lymph node metastasis other than stations no. 16a2/16b1
  (g) Other distant metastases
(iv) The macroscopic tumor type is neither the Borrmann type 4 nor large (8 cm or more) type 3
(v) No esophageal invasion or an invasion of 3 cm or less
(vi) No gastric stump cancer
(vii) No clinical signs of cervical lymph node or distant metastases
(viii) A staging laparoscopy or laparotomy performed within 28 days revealed negative washing cytology and no peritoneal metastasis
(ix) Aged between 20 and 75 years
(x) An Eastern Cooperative Oncology Group performance status of 0 or 1
(xi) No prior chemotherapy, radiotherapy or endocrine therapy for any malignancies
(xii) No prior surgery for gastric carcinoma except bypass surgery and endoscopic resection
(xiii) Fair oral intake with or without bypass surgery
(xiv) Adequate organ function
(xv) Written informed consent

Exclusion Criteria

(i) Synchronous or metachronous (within 5 years) malignancies other than carcinoma *in situ* or mucosal carcinoma
(ii) Pregnant or breast-feeding women
(iii) Severe mental disease
(iv) Currently treated with systemic steroids
(v) HBs antigen positive
(vi) Currently treated with flucytosine, phenytoin or warfarin
(vii) Iodine allergy
(viii) History of hypersensitivity to docetaxel, cisplatin or polysorbate 80
(ix) Peripheral motor neuropathy or peripheral sensory neuropathy for any reason
(x) Edema of the limbs and trunk for any reason
(xi) Interstitial pneumonia, pulmonary fibrosis or severe emphysema
(xii) Active bacterial or fungal infections
(xiii) History of myocardial infarction or unstable angina pectoris within 6 months
(xiv) Uncontrolled hypertension
(xv) Uncontrolled diabetes mellitus or routine administration of insulin.

TREATMENT METHODS

Preoperative Chemotherapy

Patients receive an infusion of docetaxel (40 mg/m^2/day) and cisplatin (60 mg/m^2/day) on day 1, and take oral S-1 (80 mg/m^2/day) for 2 weeks from days 1–14 followed by a 2-week rest period. Two courses of preoperative chemotherapy are administered unless unequivocal progression or unacceptable toxicities are observed. After the second course, the tumor response and feasibility of R0 resection are evaluated. When possible, the patient undergoes surgery within 56 days (preferably 28 days) after the last S-1 treatment. When R0 resection is considered difficult despite tumor shrinkage after the second course, the patient receives the third course of DCS before surgery.

Preoperative Examinations

Before enrollment, contrast enhanced thoracic/abdominal/pelvic CT (<10 mm slice thickness) and staging laparoscopy (or intra-abdominal exploration during bypass surgery) are mandatory to check the eligibility criteria. After the second or third course of preoperative chemotherapy, patients are evaluated by the following examinations to check the feasibility of the surgery:

(i) Contrast-enhanced thoracic CT
(ii) Contrast-enhanced abdominal/pelvic CT (the same slice width as baseline evaluation)
(iii) Staging laparoscopy is not mandatory
(iv) Tumor marker (CEA, CA19-9)
(v) Adequate organ function.

Surgery

A total or distal gastrectomy with D2 plus PAND is performed. In the total gastrectomy for an upper gastric tumor, the spleen is also removed. Involved adjacent organ(s), if any, is also removed to achieve R0 resection. A laparoscopic gastrectomy is not allowed. If resectable M1 disease (hepatic, peritoneal and/or lymphatic metastases) is found during surgery, it is removed to achieve R0 resection. If R0 resection is impossible, the protocol treatment is terminated. When total gastrectomy with thoracotomy, left upper abdominal exenteration, pancreaticoduodenectomy or Appleby's operation is required to achieve the R0 resection, the protocol treatment is terminated after the operation is completed.

Postoperative Chemotherapy

After the R0 resection, adjuvant chemotherapy with S-1 is initiated within 42 days from surgery. A 6-week course consisting of 4 weeks of daily oral S-1 administration at a dose of 80 mg/m^2/day followed by 2 weeks of rest is repeated during the first year after surgery. If S-1 treatment is not initiated within 12 weeks after surgery for any reason, the protocol treatment is terminated. Even after the R0 resection, if the tumor progressed during the preoperative chemotherapy and histological examination of the resected specimen showed no chemotherapeutic effect, the protocol treatment is terminated and S-1 is not administered.

Follow-up

All enrolled patients are followed for 5 years. Physical and blood examinations are conducted every 3 months for the first 3 years and every 6 months for the last 2 years. An abdominal CT is performed every 6 months for the first 3 years and every year for the last 2 years. Chest X-ray and upper gastrointestinal endoscopy are conducted every year.

Study Design and Statistical Analysis

This trial investigates the efficacy and safety of preoperative DCS followed by gastrectomy with D2 plus PAND and postoperative S-1. The primary endpoint is analyzed after the tumor response of all enrolled patients is evaluated. If this regimen proves promising, a Phase III trial will be designed to evaluate the superiority of preoperative DCS to preoperative S-1 plus cisplatin in terms of overall survival. In this Phase II trial, the sample size is 50 cases, which provides 80% power based on the hypothesis as the expected value of 80% and a threshold value of 65% in the primary endpoint using one-sided testing at a 10% significance level.

Interim Analysis and Monitoring

Interim analysis is not planned. The JCOG Data Center conducts data management, central monitoring and statistical analysis. If the number of TRDs reaches 3 or the number of cases with R1/R2 resection reaches 13, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves the continuation of this trial.

PARTICIPATING INSTITUTIONS

Hakodate Goryoukaku Hospital, Iwate Medical University, National Hospital Organization, Sendai Medical Center, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo Medical and Dental University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo Metropolitan Bokutoh Hospital, Kanagawa Cancer Center, Kitasato University School of Medicine, Yokohama City University Medical Center, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Tsubame Rosai Hospital, Toyama Prefectural Central Hospital, Ishikawa Prefectual Central Hospital, Gifu University Hospital, Gifu Municipal Hospital, Shizuoka General Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, National Hospital Organization Kyoto Medical Center, Osaka University Graduate School of Medicine, Kinki University School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka National Hospital, Osaka Medical College, Toyonaka Municipal Hospital, Sakai Municipal Hospital, Kansai Medical University Hirakata Hospital, Kobe University Graduate School of Medicine, Kansai Rosai Hospital, Hyogo College of Medicine, Hyogo Cancer Center, Itami City Hospital, Wakayama Medical University School of Medicine, Shimane University School of Medicine, Hiroshima City Hospital, Hiroshima City Asa Hospital, Fukuyama City Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Science Center and Oita University Faculty of Medicine.

Funding

This study is supported by the National Cancer Center Research and Development Fund (23-A-16, 23-A-19) and the Health and Labour Sciences Research Grant for Clinical Cancer Research (H22-Gan-016) from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest statement

Mitsuru Sasako and Takeshi Sano state that they have received honoraria from Taiho Pharmaceutical Company for promotion of education and research in 2011.

References

1. Yoshikawa T, Sasako M, Yamamoto S, et al. Phase II study neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Sur* 2009;96:1015–22.
2. Yoshikawa T, Nakamura K, Tsuburaya A, et al. A phase II study of preoperative chemotherapy with S-1 and cisplatin followed by D3 gastrectomy for gastric cancer with extensive lymph node metastasis: survival results of JCOG0405. *Am Soc Clin Oncol* 2011 (Gastrointestinal Cancers Symposium Abstract No. 70).
3. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;359:453–62.
4. Sasako M, Mcculloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. *Br J Surg* 1995;82:346–51.
5. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;24:4991–7.
6. Sato Y, Takayama T, Sagawa T, et al. Phase II study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. *Cancer Chemother Pharmacol* 2010;66:721–8.
7. Fushida S, Fujimura T, Oyama K, Yagi Y, Kinoshita J, Ohta T. Feasibility and efficacy of preoperative chemotherapy with docetaxel, cisplatin, and S-1 in gastric cancer patients with para-aortic lymph node metastases. *Anticancer Drugs* 2009;20:752–6.
8. Nakayama N, Koizumi W, Sasaki T, et al. A multicenter, phase I dose-escalating study of docetaxel, cisplatin and S-1 for advanced gastric cancer (KDOG0601). *Oncology* 2008;75:1–7.
9. Koizumi W, Nakayama N, Tanabe S, et al. A multicenter phase II study of combined chemotherapy with docetaxel, cisplatin and S-1 in patients with unresectable or recurrent gastric cancer (KDOG 0601). *Cancer Chemother Pharmacol* 2012;69:407–13.

Gastric Cancer (2012) 15:206–212
DOI 10.1007/s10120-011-0099-0

ORIGINAL ARTICLE

Intra-abdominal infectious complications following gastrectomy in patients with excessive visceral fat

Norihiko Sugisawa · Masanori Tokunaga · Yutaka Tanizawa · Etsuro Bando · Taiichi Kawamura · Masanori Terashima

Received: 15 May 2011 / Accepted: 11 September 2011 / Published online: 13 October 2011

Abstract
Background Excessive visceral fat may be a better predictor of the development of postoperative morbidity after gastrectomy than body mass index (BMI). The aim of the present study was to clarify the most appropriate fat parameter to predict pancreas-related infection and anastomotic leakage following gastrectomy.
Methods The study was performed in 206 patients who underwent curative gastrectomy at the Shizuoka Cancer Center between April 2008 and March 2009. Relationships between fat parameters, including visceral fat area (VFA), and early surgical outcomes were investigated. The risk factors for pancreas-related infection and anastomotic leakage were identified using univariate and multivariate analyses.
Results There was no strong association between any of the fat parameters and operating time, intraoperative blood loss, the number of lymph nodes retrieved, or the duration of the postoperative hospital stay. Pancreas-related infection occurred in 18 patients (8.7%), whereas anastomotic leakage was observed in 10 patients (4.9%). Of all the fat parameters, only VFA was found to be an independent risk factor for both pancreas-related infection and anastomotic leakage, with odds ratios (95% confidence intervals) of 1.015 (1.005–1.025) and 1.010 (1.000–1.021), respectively.
Conclusions Excessive visceral fat, represented by the VFA, was found to be an independent risk factor for both pancreas-related infection and anastomotic leakage following gastrectomy.

N. Sugisawa · M. Tokunaga · Y. Tanizawa · E. Bando · T. Kawamura · M. Terashima (✉)
Division of Gastric Surgery, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: m.terashima@scchr.jp

Keywords Gastric cancer · Gastrectomy · Visceral fat · Postoperative complication

Introduction

Surgery is the only treatment strategy that offers the hope of a cure for gastric cancer patients. In Japan, in which the rates of gastric cancer are greater than those in Western countries, gastrectomy with D2 lymph node dissection is a well-established and widely accepted procedure [1, 2]. Although two large randomized controlled trials in Europe failed to demonstrate the efficacy of this procedure, due, in part, to increased postoperative morbidity and mortality [3, 4], recent reports suggest that gastrectomy with D2 lymph node dissection may be beneficial in certain patients [3–6]. One of the reasons for the unfavorable outcomes of gastrectomy with D2 lymph node dissection in the European studies may have been the higher proportion of obese patients in those studies.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify obesity. In Japan, the median BMI of gastric cancer patients, as well as that of the general population, has increased in recent years [7]. Although a relationship between BMI and postoperative morbidity has been reported previously, it remains contentious whether a high BMI is really associated with an increased rate of postoperative morbidity [8–12]. Recently, several reports have suggested that visceral fat area (VFA) is more strongly associated with postoperative intra-abdominal infectious complications, including pancreas-related infection and anastomotic leakage, than BMI [13, 14]. However, this issue is also contentious.